# Ultrasonography in Regenerative Injection (Prolotherapy) Using Dextrose, Platelet-rich Plasma, and Other Injectants

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**KEYWORDS**

- Ultrasonography • Prolotherapy • Platelet-rich plasma
- Tendinopathy

Imaging modalities in musculoskeletal medicine assist with diagnosis and ideally lead to an effective course of treatment that improves function at reasonable cost. Adoption of a specific imaging modality often depends on the intervention being considered. For example, magnetic resonance imaging (MRI), assists physicians in distinguishing surgical versus nonsurgical lesions. However, MRI may also lead to unnecessary intervention in cases such as degenerative meniscal tears and lumbar disc degeneration.[1,2] Musculoskeletal ultrasonography (MSKUS) is in its infancy and may be subject to the same type of misapplications. However, MSKUS has several advantages compared with MRI, such as low cost, high patient tolerability, real-time imaging to correlate with symptoms, and superior resolution in soft tissues.[3] Borg-Stein and colleagues[4] recently reviewed new concepts in assessing and treating musculoskeletal sports injury. This article summarized the benefits of MSKUS in evaluating soft tissue injury. The investigators also discussed injection therapies that are proposed to stimulate repair in these same tissues. A brief history may help in understanding the nomenclature of these interventions.

In the 1930s, Schultz[5] reported on an injection technique that successfully induced tightening of loose temporomandibular joints; the solution injected was derived from

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the psyllium seed. In the 1950s, Hackett[6] named this technique prolotherapy to imply proliferation of fibrous tissue. In his monograph, Hackett[6] described the use of prolotherapy in the treatment of chronic low back pain. In the early 1990s, the monograph was updated with articles on proposed mechanism of action and use of prolotherapy (using other injectants, such as dextrose and morrhuate sodium) in essentially all joints of the body. Since those early reports in the treatment of temporomandibular joint syndrome and low back pain, the clinical use of prolotherapy has outpaced the research evidence for its use. Multiple texts have now been produced with detailed descriptions of prolotherapy technique that usually involves a diffuse pattern of injection[7–9] and avoidance of antiinflammatory medications during treatment. The rationale for a diffuse injection pattern is based on the interconnected network of soft tissue (ie, fascia) that supports all joint structures. Rather than being a shotgun approach with the hope of injecting the correct structure, this technique is theorized to initiate a more vigorous response from the body to heal these fascial networks. These theories are discussed in more detail later in this article.

More recently, prolotherapy has been defined as the injection of growth factors or growth factor production stimulants, to promote growth and repair of normal cells and tissue.[10] This global definition of prolotherapy is used in this article. A proliferant is any solution injected with the intent of growth or repair. The growth factors produced or provided with proliferant injection are those that are increased during the repair phase in soft tissue of various types, and thus connective tissue is the target for treatment.[11] Linetsky and colleagues[12] proposed the term regenerative injection therapy to describe treatments with this goal.

In the late 1990s, surgeons began adding platelet-rich plasma (PRP) to fibrin glue, forming a gel to place in surgical sites.[13] The goal was to improve healing, anchoring of implantable hardware, and speed of recovery. In the early part of this century, individual physicians began injecting PRP as a prolotherapy agent (Michael Scarpone, MD, personal communication, 2010). The first published, nonsurgical report was a case series published in the podiatry literature.[14] Foster and colleagues[15] recently reviewed the basic science of PRP and its emerging application in surgical and nonsurgical sports medicine. In this article, Foster and colleagues[15] report unpublished data on ultrasound-guided PRP injection of medial collateral ligaments in the knee and acute muscle tears. Crane and Everts[16] believe the clinical use of PRP at this time has been most commonly applied by physicians previously trained in prolotherapy technique. We have a total of greater than 30 years clinical experience with dextrose and other nonautologous agents and 4 years experience using autologous PRP as an injectant.

Since 2005, the Hackett-Hemwall Foundation (a nonprofit organization supporting training and medical missions focused on prolotherapy) and the University of Wisconsin have sponsored an annual research forum focused on regenerative injection treatments. The mode of action for these therapies has been a major focus of discussion. Banks[17] has proposed that the common end point of prolotherapy is formation of new collagen fibers. He believes that this primarily occurs through the induction of inflammation after injection of various substances: osmotic fluids, irritants, particulates, or chemotactic agents. However, growth factor effects can occur with neither an injectant nor inflammation. For example, clinical trials in which needling with injection of normal saline were used as a control have resulted in substantial and sustainable improvement in chronic pain, indicating that the process of needling is likely an active treatment.[18–20] Growth factor stimulation by lipids released from cell membrane rupture and microbleeding with release of platelets have been proposed as potential mechanisms for such an effect.[11] Not only is needling alone potentially an active treatment but inflammation may not be essential either, in that production of growth factors for soft tissue begins promptly after exposure of a variety of human cells to dextrose at levels of only 0.6%.[11] Presentations at the Wisconsin meetings related to mechanism of action have varied from the original model of inflammation induction of the healing cascade, to focusing on the body's response to percutaneous needling/tenotomy, perineural injection of hyperosmolar dextrose in fascial planes, sclerosing of abnormal neovessels in tendinopathy, partial neurolysis through the inclusion of phenol in solutions, dextrose-induced release of growth factors, and more direct forms of growth factor injection such as PRP.

Rabago and colleagues[21] discuss many of these proposed mechanisms of action in their review of 4 injection therapies for lateral epicondylosis (LE). They conclude that "there is strong pilot-level evidence supporting the use" of dextrose/sodium morrhuate, polidocanol, autologous whole blood, and PRP injections in the treatment of LE. The common goal of these injection treatments is to stimulate a normal tissue repair cascade resulting in organized collagen fibers, not scar. The evidence base showing regeneration of tissue with these methods is small but growing at this point. Ultrasonography provides a low-cost method of evaluating soft tissue organization, function, and density more objectively. This article focuses on the use of ultrasound to identify soft tissue pathology, then objectively evaluates tissue repair after treatment with prolotherapy as defined earlier. As discussed elsewhere in this issue, abnormal fibrous tissue on ultrasound is generally less echoic, less organized/more heterogeneous (ie, loss of fibrillar pattern on longitudinal imaging), and thicker than normal fibrous tissue. If an intervention results in regeneration of normal tissue, the tissue should progressively return toward normal echogenicity, show return of normal fibrillar pattern, and return toward normal thickness.

The ultrasonography images in this article are from Dr Fullerton's practice. Protocol for all follow-up imaging includes reproducing exact machine settings from the initial examination, then reproducing the exact slice and probe angulation of the previous examination as closely as possible, using bone landmarks as a guide.

## LITERATURE REVIEW WITH ULTRASONOGRAPHY CASE EXAMPLES

In 1993, Robert Schwartz, MD, a physiatrist, published the first known report using ultrasonography to evaluate tissue changes after prolotherapy.[22] A 32-year-old woman had persistent hand and wrist pain 17 weeks after a fall on her outstretched left wrist. Her symptoms had not resolved with nonsteroidal antiinflammatory drugs (NSAIDs), watchful waiting, or physical therapy. An ultrasound scan at that time revealed irregularity, discontinuity, and hypoechogenicity at the ulnar collateral and dorsal intercarpal ligaments. She was treated with a solution of 0.5 mL morrhuate sodium and 1 mL of 1% lidocaine injected at ligamentous entheses. Three treatments resulted in 75% long-term improvement and a return to a normal signal on ultrasound. At this time, most ultrasound evidence supporting prolotherapy is in the form of case reports, such as Dr Schwartz's, or case series focused on specific diagnoses that are reviewed in this article. Large controlled studies using ultrasonography as an outcome measure require development of quantitative ultrasound tools that could be used in a blinded fashion, as discussed later in this article.

### *Elbow Tendinosis*

Since 2001, South Korean researchers have published 21 articles on dextrose prolotherapy,[23] and 3 of these reported use of ultrasonography in conjunction with prolotherapy. Although the full papers are published in Korean only, the abstracts, tables, and figures are available in English. Shin and colleagues[24] reported that 71 of 84 patients with LE of the elbow showed statistically significant reductions in pain measured by visual analog scale (VAS). Forty-nine of these patients underwent MSKUS before treatment. Patients without clear partial tendinous tear on ultrasonography had more significant reduction in pain than those with a tear, indicating a possible predictive benefit of MSKUS. Park and colleagues[25] reported on 12 common extensor tendons in 11 patients with LE of the elbow (tennis elbow). All had partial tears described as anechoic regions within the tendon; 1 was a full thickness but incomplete width tear. All patients were treated with dextrose prolotherapy (2–6 treatments) and had follow-up ultrasound 4.5 to 6.5 months after the initial ultrasound. All patients responded to treatment with reductions in pain on VAS. The most salient evidence of change on ultrasound was reappearance of a fibrillar pattern in the initially anechoic region in all 11 tendons. Kang and colleagues[26] also reported on 12 LE patients with partial tears of the common extensor tendon. All were treated with 5 monthly injections of 15% dextrose. Five of the 12 had tears without evidence of tendinosis before treatment; none of these showed tendinosis on follow-up ultrasonography. Seven of the 12 had tears with tendinosis before treatment; 5/7 of these did not show tendinosis on follow-up examination. All showed appearance of fibrillar pattern in the anechoic regions after treatment. In the English language literature, Louis[27] reported a case of common extensor repair on ultrasound after dextrose prolotherapy.

We see similar changes on ultrasonography in our clinics; an example has been published in a sports medicine text.[11] An example of common flexor tendon tear in the elbow is included here (**Fig. 1**). The patient is a 40-year-old man with 9-year history

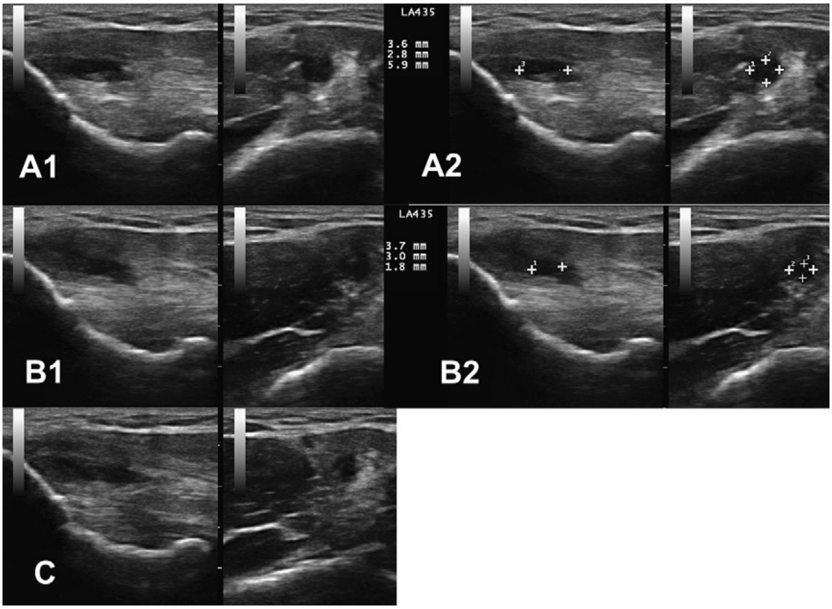

**Fig. 1.** Common flexor tendon tear in a 40-year-old retired, professional baseball player. (*A1*, *A2*) Without and with measurements of the tear that contributed to his early retirement. (*B1*, *B2*) Four weeks after 1 treatment with 15% dextrose injection via 27-gauge, 3.2-cm needle. (*C*) Four weeks after the second treatment. The third treatment was performed at that appointment and his chronic medial elbow resolved.

of medial elbow pain. He retired early from professional baseball after developing problems with throwing accuracy. During his career, he was treated with 4 corticosteroid injections for medial epicondylitis diagnosed by MRI; these were not successful. In our clinic, he received 3 treatments with 15% dextrose to the common flexor tendon and ulnar collateral ligament. The tear reduced significantly in size and developed a fibrillar pattern within the anechoic region. The patient reported significant reduction in pain and returned to weight lifting, which he had not been able to tolerate before treatment.

In 2006, Mishra and Pavelko[28] published the first study on the use of PRP injection in chronic tendinopathy. This study is summarized elsewhere in this issue. No imaging before or after treatment was reported and ultrasound guidance was not used. A case of PRP treatment in severe LE is included in **Fig. 2**. This 45-year-old man had a history of bilateral chronic LE resulting in surgical tenotomy on the right and multiple

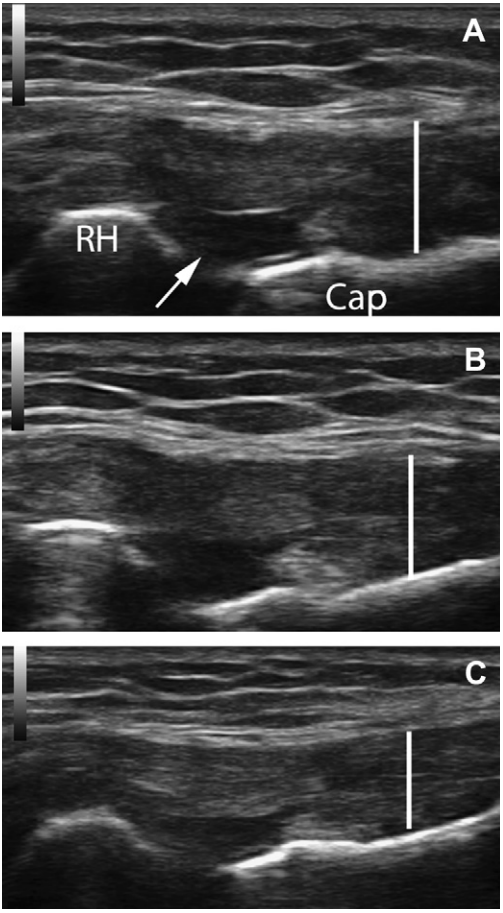

**Fig. 2.** Advanced LE in a 45-year-old man. (*A*) Poorly organized common extensor tendon (white line indicates thickness of the tendon) with minimal fibrillar pattern and tear in the joint capsule/radial collateral ligament (*arrow*). (*B*) Follow-up imaging after one 15% dextrose and one PRP treatment. (*C*) Follow-up after second PRP treatment showing return of fibrillar pattern in the tendon and joint capsule. Cap, capitellum; RH, radial head.

steroid injections bilaterally. He was treated with 1 dextrose prolotherapy followed by 2 PRP treatments with almost complete resolution of symptoms; he returned to playing golf for the first time in 2 years. The clinical improvement in this patient has now been maintained for 8 months. Movie 1 shows the first injection of PRP confirming capsular tear as the hyperechoic PRP flows through the tendon into the radiocapitellar joint. Clinical observations such as this illustrate the potential of ultrasonography to expand understanding of pathophysiology in tendinopathy.

### *Osteitis Pubis*

In 2005, Topol and colleagues[29] reported a consecutive case series involving elite Argentinean athletes with chronic groin pain (6–60 months). Athletes were diagnosed with osteitis pubis, abdominal tendinopathy at the pubic bones, and/or hip adductor tendinopathy based on history, clinical examination, and response to lidocaine blockade at the corresponding entheses. Athletes received a mean of 2.8 treatments of 12.5% dextrose with 0.5% lidocaine. Twenty-two of 24 athletes who had been unable to participate in their sport returned to full play; 20/24 had complete resolution of symptoms with full sport. The same investigators extended the case series to 72 athletes by 2008.[10] Sixty-six of 72 returned to unrestricted sports activity with minimum follow-up of 3 years after completion of treatment. No imaging was included in these studies. An example of pre- and posttreatment images of the pubic symphysis is included in **Fig. 3**. The patient is a 55-year-old man with a 3-year history of pubic/groin pain and pubic symphysis crepitus after impact between the pubic symphysis and a saddle horn when his horse stumbled. After 3 treatments with dextrose/morrhuate sodium injection at the superior pubic ligament, his VAS reduced from 6 to 0.

### *Patellar Tendinopathy*

In 2008 Volpi and colleagues[30] evaluated a single PRP treatment combined with structured rehabilitation protocol in chronic patellar tendinosis. A total of 10 tendons in 7 athletes were treated and completed follow-up. Ultrasound was used for guidance in the injection of 3 mL of autologous PRP spread between 5 and 8 locations using a 22-gauge needle. Eight of the 10 tendons examined with MRI at follow-up showed “signs of reduced irregularity at the level of the tendon insertion and the preinsertional eodema” compared with pretreatment MRI findings. Ultrasound was not used in pre- or posttreatment evaluation. All subjects completing the study showed a considerable (more than 35-point) improvement in the Victorian Institute of Sport Assessment (VISA) score, a measure of function and sports performance.

In 2009, Kon and colleagues[31] published a pilot study using a series of 3 PRP treatments followed by rehabilitation for jumpers knee. Twenty male athletes had pretreatment imaging with MRI or MSKUS to confirm the diagnosis. They received 5 mL of autologous PRP at each treatment with 15 days between each session. At 6-month follow-up, 16/20 (80%) were satisfied with treatment and showed statistically significant improvements in SF-36 parameters and sports activity ($P$ = .002–0.0005); 4/20 (20%) did not improve.

Ultrasonographic follow-up after prolotherapy for patellar tendinopathy has been reported in 2 case reports; both included pre- and posttreatment ultrasonography. One included MRI confirmation of the improvements on ultrasound (ie, improved fibrillar pattern and echogenicity, reduction in tear, resolution of patellar edema) after treatment with 15% dextrose (×3) and 1 treatment with Ongley solution (phenol, glycerin, glucose).[32] Louis[27] showed significant reduction in neovascularization after injection of 25% dextrose.

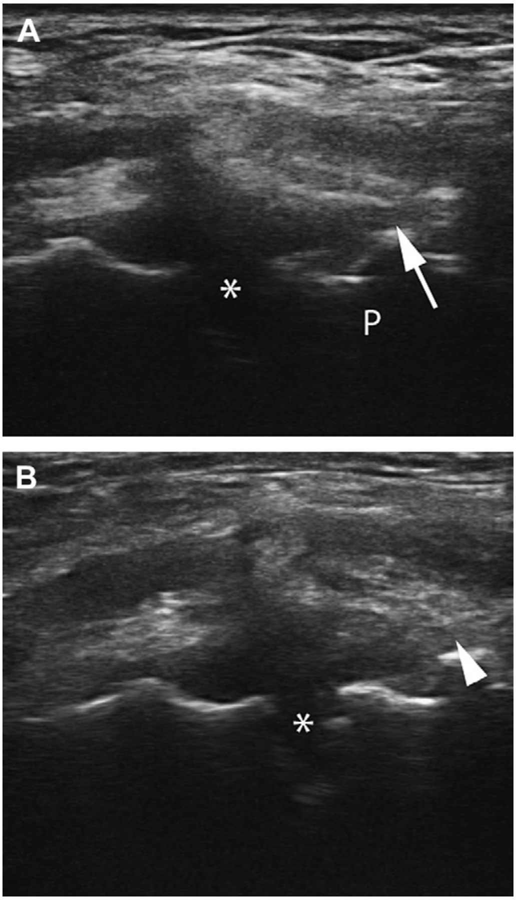

**Fig. 3.** Osteitis pubis in a 55-year-old man with chronic groin pain. (*A*) Pubic symphysis (*asterisk*) with superior pubic bone on either side (P). (*Arrow*) Superior pubic ligament with heterogeneous echotexture and loss of fibrillar pattern. (*B*) Follow-up image 6 weeks after third treatment with dextrose/morrhuate sodium prolotherapy; the chronic pain had resolved. Echogenicity is markedly improved and fibrillar pattern has returned (*arrowhead*).

### *Achilles Tendinopathy*

In 2005, Lazzara[33] reported repair of an Achilles tendon rupture using dextrose/morrhuate sodium prolotherapy. The 26-year-old female soccer player was initially diagnosed with severe calf sprain and treated with cast in 30° plantar flexion. MRI at day 43 after the injury revealed a complete tear of the Achilles tendon with a 1.1-cm gap. She refused surgical repair and presented to Dr Lazzara requesting a trial of prolotherapy. She received treatment every other week for a total of 8 treatments using dextrose and morrhuate sodium and returned to sports without pain or limitation. Repeat MRI after the sixth treatment showed “no abnormality distal to the musculotendinous junction.” The pre- and posttreatment sagittal MRI images do show improved tendon signal, but do not show the same slice of tendon. The pretreatment ultrasound image does not show a clear tendon tear. Pre- and posttreatment ultrasound images lack scale or bony landmarks to orient the viewer, making the imaging unconvincing.

In 2007, Sanchez and colleagues[34] reported on the use of PRP to facilitate healing after surgical repair of ruptured Achilles tendon. Six athletes underwent open suture repair with addition of a preparation rich in growth factors (PRGF), another term for PRP. Those were compared retrospectively with matched controls (same mechanism of injury, age, gender, activity) undergoing the repair without addition of PRGF. Each group received oral diclofenac as needed after the procedure. Ultrasonographic follow-up was performed on each group. The PRGF group showed less increase in cross-sectional area of the tendon, which indicates more tightly packed collagen fibers. The PRGF group had no wound complications, recovered range of motion earlier, and returned to gentle running and training sooner than the control group.

De Vos and colleagues[20] recently examined the effects of 1 PRP treatment compared with saline injections under ultrasound guidance in 54 patients with chronic Achilles tendinopathy. Both groups improved significantly; however, there were no differences between the 2 groups. Patient selection was a significant limitation of this study. Patients were not required to try standard-of-care treatment (eccentric exercise) before injection; and all patients performed eccentric exercise after injection. Insertional Achilles tendinopathy was excluded; although this type of injury responds well in our experience, as seen in the example discussed later. Ultrasound was also not used to describe the extent of tendinopathy; there are no descriptions of tears, neovascularization, or extent of inhomogeneous regions. The saline injection should not be considered a placebo because it involved multiple intratendinous insertions, and the body responds to needle tenotomy and stretching of fibers from volume injection. The only conclusion from this study is that injections do not need to be given before trying noninvasive, standard-of-care treatment in patients with proximal Achilles tendinopathy.

In 2007, Maxwell and colleagues[35] reported on 36 consecutive patients with chronic Achilles tendinopathy treated with ultrasound-guided injection of hyperosmolar (25%) dextrose. Mean percentage reduction in pain VAS was significant: 88.2% at rest, 84% with daily activity, and 78.1% with sport or other high-level activity. This prolotherapy study is the largest that has included before and after ultrasonography as an outcome measure. The investigators reported a highly significant ($P = .0007$) improvement (reduction) in mean tendon thickness, from 11.7 to 11.1 mm, between initial and follow-up ultrasounds. Posttreatment tendons with anechoic clefts or foci reduced by 78%. Neovascularity decreased in 55% of tendons; it was unchanged in 33% of tendons. Four tendons had no neovascularity before or after treatment. Echogenicity was unchanged in 82% of tendons and improved in 18% (this finding is discussed later). Twelve-month phone follow-up (mean) was conducted in 30 available patients: 20 were still asymptomatic, 9 had mild symptoms, and 1 had moderate symptoms.

**Fig. 4**A to C and **Fig. 5**A to C show tissue changes after dextrose prolotherapy in a 67-year-old man with insertional, calcific Achilles tendinopathy and a partial tear. These images show significant, but not complete, repair of a partial tear in the setting of advanced tendinosis using 25% dextrose prolotherapy delivered via a 27-gauge needle. Movie 2 (from the first of 5 dextrose treatments) shows a transverse view of the tendon with injection at the tear. Hyperechoic debris filters from within the intact portion of the tendon through the tear. These images illustrate the importance of imaging in 2 planes. **Fig. 4** (longitudinal imaging only) gives the impression that the tear is fully repaired after 3 treatments with 15% dextrose (images A to B). However, these sagittal images through the tendon are not of the same slice. **Fig. 5**, which includes transverse images, shows that the tear is reduced, but not completely resolved. **Fig. 4**D and **Fig. 5**D show additional tissue changes after tenotomy using a 16-gauge needle with injection of PRP. Movie 3 is a longitudinal view at the Achilles

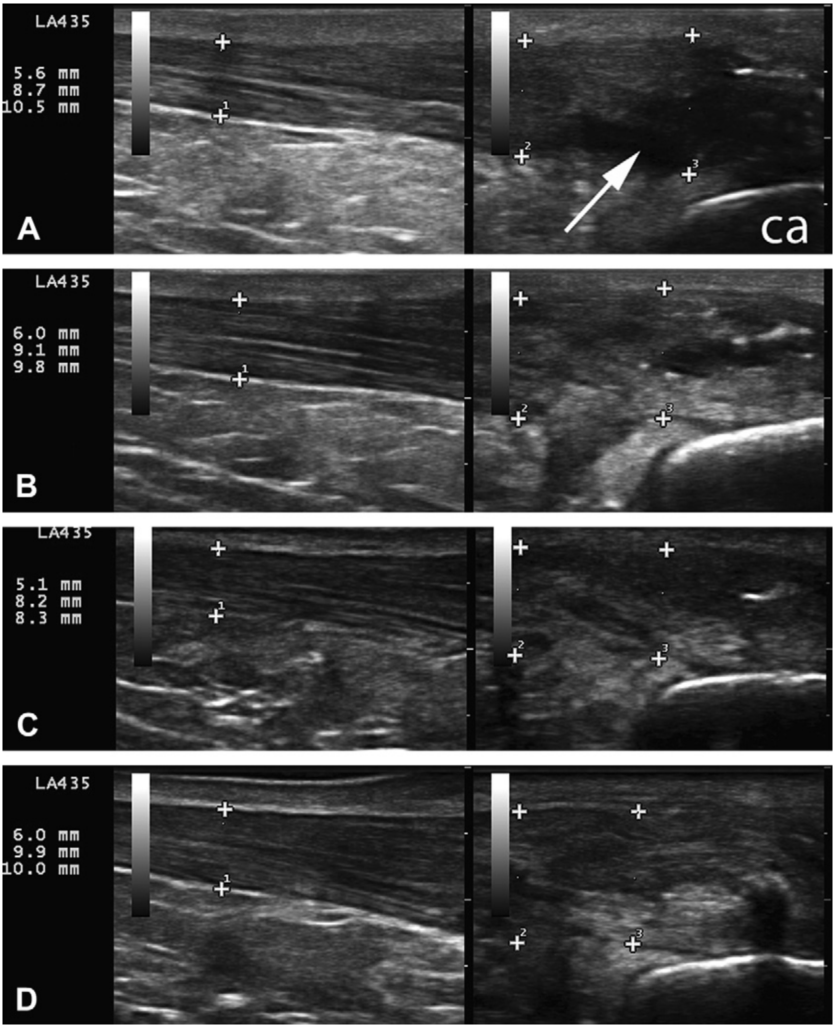

**Fig. 4.** Sixty-seven-year-old man with insertional Achilles tendinopathy with tear. (*A*) Compound image of Achilles tendon with proximal (*left*) tendon showing good fibrillar pattern. (*Right*) The field of view extended to the calcaneal insertion (*ca*) showing marked thickening, loss of fibrillar pattern, and anechoic tear (*arrow*). (*B*) Six weeks after third treatment with dextrose prolotherapy showing apparent resolution of the tear. Fig. 5 disproves this assumption (see text). (*C*) After 2 more treatments with dextrose prolotherapy. (*D*) Eight weeks after percutaneous tenotomy and PRP injection.

insertion, showing the needle tenotomy with injection at regions of calcification. The patient elected for this more aggressive treatment of calcific regions in an attempt to resolve all symptoms. Now, 8 months after percutaneous tenotomy with PRP, he is pain free with all activities.

### *Plantar Fasciitis/Fasciosis*

In 2004, the podiatrists Barrett and Erredge[14] reported a case series of ultrasound-guided, autologous PRP injection for plantar fasciitis. Nine patients with diagnosis

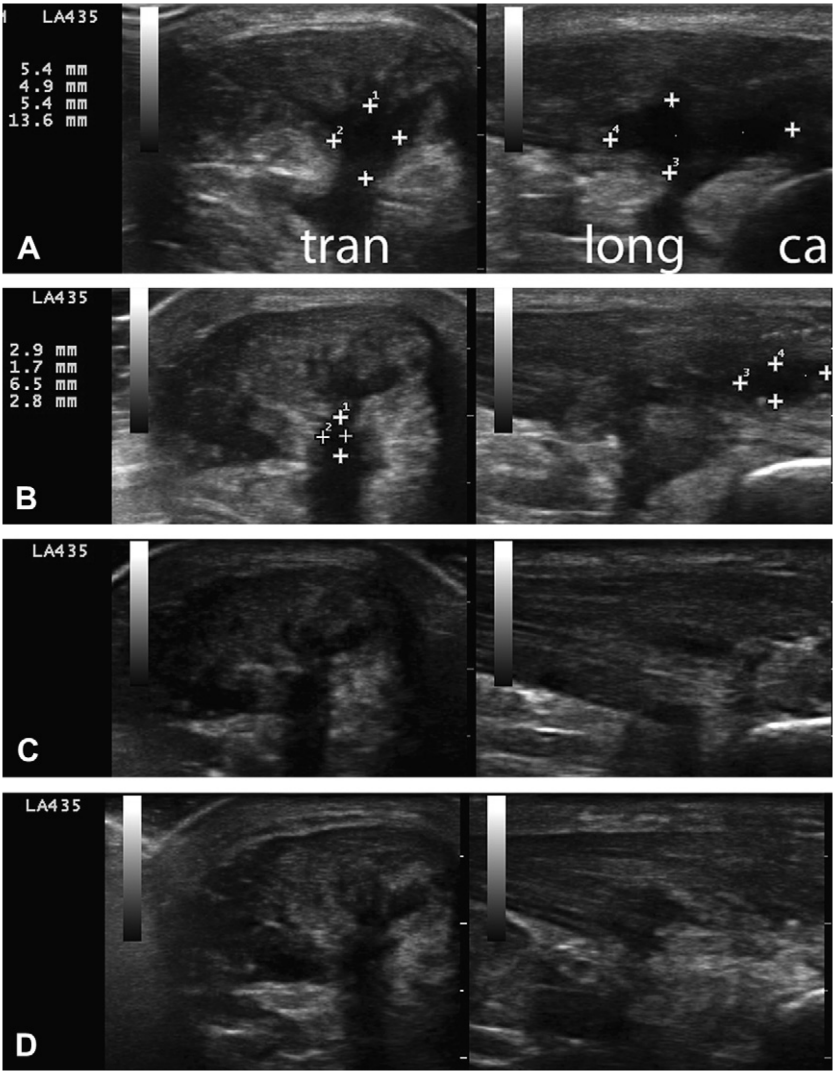

**Fig. 5.** Same patient as **Fig. 4**. (*A*) Diffuse heterogeneous signal on transverse (*left*) and longitudinal (*right*) images with 13.6 × 5.4 × 4.9 mm tear. (*B*) Six weeks after 3 treatments with 15% dextrose showing significant reduction in the tear. (*C*, *D*) After further treatment as described in **Fig. 4**. **Fig. 4** and this figure show progressive return of normal fibrillar pattern, homogeneous echotexture, and almost complete resolution of the tear in a degenerative tendon. They also illustrate the importance of 2-plane imaging to characterize pathology accurately.

of plantar fasciitis (fasciosis) were recruited; all had "significantly thickened and hypoechoic plantar fascia" on MSKUS using high-frequency linear array transducer. Under ultrasound guidance, 3 mL of PRP was injected at the most hypoechoic regions. Sequential ultrasound scans were obtained at 1 week, 2 weeks, 4 weeks, and 3 months. All 9 patients showed improvement on ultrasound with increased signal intensity and an average reduction in thickness of more than 2 mm. Six of the 9 obtained complete resolution of symptoms 2 months after 1 treatment. One of these was dropped from the study after receiving a subsequent steroid injection. Two of the 9 had complete resolution of symptoms after a second treatment with PRP. One of the 9 had occasional pain when walking barefoot.

Louis[27] included an example of plantar fasciitis with partial tear in his review article of musculoskeletal ultrasound intervention. Ultrasound before dextrose prolotherapy shows the classic appearance of plantar fasciitis with partial tear at the deep insertion. The image after treatment shows a thinner plantar fascia with improved echogenicity, improved fibrillar pattern, and almost complete resolution of the tear. This concurs with our clinical experience using dextrose injection to treat plantar fasciopathy. **Fig. 6** shows an example of tissue changes in a 58-year-old woman with a 2-year history of symptomatic plantar fasciopathy unresponsive to standard-of-care treatment. After 3 treatments with 25% dextrose, her VAS dropped from 7 to 0 with all activities.

In 2009, Ryan and colleagues[36] published a pilot study on ultrasound-guided injection of hyperosmolar dextrose for chronic plantar fasciopathy. Patients unresponsive to standard treatment were injected with 25% dextrose at hypoechoic regions within the plantar fascia. After 3 treatments, 16/20 patients (80%) reported good to excellent results with significant reduction in pain VAS at rest, with activities of daily living and after physical activity. Four of the 20 patients (20%) were unchanged after treatment. Ultrasonographic follow-up was not reported. Twelve of the 20 patients continued to be asymptomatic and 4/20 had pain reduction of more than 75% at a phone follow-up time of 6 to 20 (mean 11) months.

### *Osteoarthrosis*

In 2000, Reeves and Hassanein[37] published a double-blind randomized trial in finger osteoarthrosis. Treatment involved 10% dextrose/0.87% lidocaine/0.03% benzyl

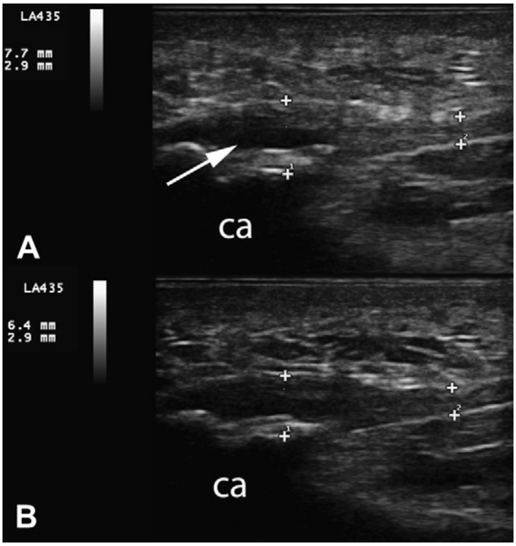

**Fig. 6.** Fifty-eight-year-old woman with chronic plantar fasciosis. (*A*) The plantar fascia (*outlined with cross-hairs*) in longitudinal view. A tear is viewed (*arrow*) near the calcaneal insertion (ca). (*B*) Six weeks after third treatment with 15% dextrose showing increased signal in the tear and reduction of thickness from 7.7 to 6.4 mm.

alcohol injection versus a control solution that was identical except without dextrose. From 0.25 to 0.5 mL of either solution was injected into the medial and lateral joint capsules of symptomatic joints. Treatments at 0, 2, and 4 months resulted in clinically and statistically significant improvement favoring the dextrose group in joint pain ($P = .027$) and range of motion ($P = .007$). The study did not include ultrasonographic examination; however, future studies could include pre- and posttreatment imaging, as in **Fig. 7**, showing improved echogenicity in the joint capsule after dextrose prolotherapy.

Reeves and Hassanein[38] also published a double-blind placebo-controlled study on dextrose prolotherapy treatment in knee osteoarthrosis. Treatment was similar to the small joint study, except injection was only intraarticular rather than capsular. Although the dextrose group responded better in multivariate analysis ($P = .015$), benefits in the control group in pain, range of motion, and knee buckling episodes were considerably more than a placebo response, suggesting that the hypoosmolarity (mOsm 105), or some other quality of the control solution, resulted in clinical benefit. Future studies with the use of ultrasound to measure femoral cartilage thickness at the suprapatellar, femur with flexed knee position, may be of interest.

Kon and colleagues[39] reported results of a large, prospective case series using intraarticular PRP injection in patients with degenerative chondral lesions of the knee seen on MRI (Kellgren 0, n = 58 knees) or clear osteoarthrosis on radiograph (Kellgren I–III, n = 33; Kellgren IV, n = 24). Injection of 5 mL PRP (via lateral approach without guidance) occurred every 21 days for a total of 3 treatments. CaCl was added to activate platelets. Statistically significant improvements were seen in clinical measures ($P<.0005$) at 6 and 12 months. No follow-up imaging was reported.

Typical prolotherapy technique with dextrose includes injection of multiple extraarticular structures (in addition to the intraarticular injection) that are easily accessible with MSKUS, such as the peripheral medial meniscus and adjacent medial collateral ligament. A case report has been published showing repair of a complex degenerative

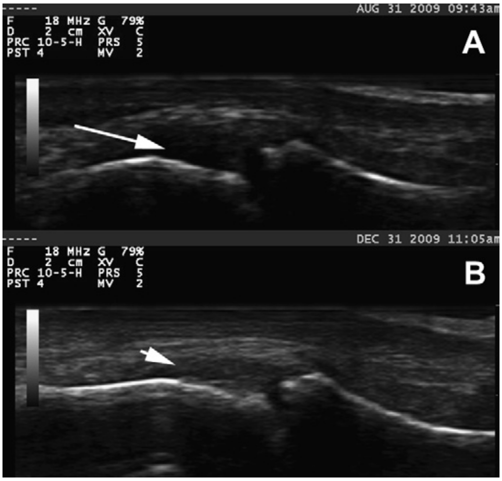

**Fig. 7.** Fifty-six-year-old woman with history of finger osteoarthrosis. (*A*) Second proximal interphalangeal with early arthritic changes, showing the proximal joint capsule (*arrow*), which is hypoechoic. (*B*) Six weeks after third treatment with 15% dextrose, showing the same location with improved echogenicity and fibrillar pattern (*arrowhead*). Her symptoms of crepitus and mild pain resolved completely.

medial meniscus tear in a 59-year-old woman.[32] The ultrasound findings were confirmed before and after treatment on MRI. Some investigators consider meniscus degeneration to be the earliest finding of knee osteoarthrosis.[40] Prolotherapy treatment of degenerative meniscus may be an area of future research. In the author's experience, these patients also show degenerative changes in the medial collateral ligament. **Fig. 8** shows progressive improvement after dextrose and morrhuate sodium prolotherapy in a medial collateral ligament that contains a meniscal cyst.

## ULTRASONOGRAPHY IN TENDON RESEARCH

In 1993, Martinoli and colleagues[41] showed that the fiber organization seen on ultrasound reflects the histologic organization of collagen fibers. Van Holsbeek[42] argued that ultrasound has significant advantages compared with MRI in evaluating the internal architecture of the tendon. As shown earlier, repair of the Achilles tendon in response to dextrose and PRP injection can be visualized on ultrasonography in individual cases; however, descriptive cases are subject to wide variation in interpretation based on the examiner's experience and biases. Quantitative measures with intrarater and interrater reliability are needed for high-quality MSKUS research. Quantification efforts are scattered through the medical literature, ranging from simple measures of structure thickness to highly complex mathematical models using computerized analysis to grade tissue organization.

### *Semi-quantitative Measures*

Initial efforts to quantify ultrasound findings have focused on simple measurement of tendon thickness in the long or short axis, as in the study by Maxwell and colleagues.[35] This becomes more problematic in tendons that curve as they insert, such as rotator cuff tendons. Simple measures of thickness also are a problem when there are tears within a region of tendinopathy, which is also common in rotator cuff pathology. A healing response could theoretically remodel and thin the region of tendinosis while

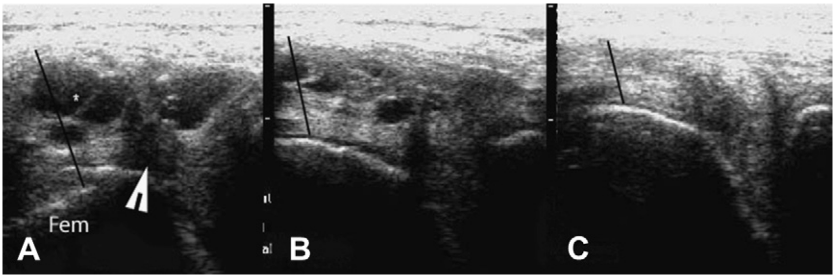

**Fig. 8.** Fifty-one-year-old man with history of knee osteoarthrosis and 6 years of knee pain. (*A*) Medial knee joint with femur (*Fem*) at left. The meniscus is the triangle of white signal to the right of the white arrowhead. There is a tear (*arrowhead*) in the meniscofemoral portion of the medial collateral ligament (MCL). Fluid has leaked into the layers of the MCL forming a meniscal cyst. The black line defines the width of the MCL containing the cyst. (*B*) Six weeks after a third prolotherapy treatment (2 with 15% dextrose; 1 with dextrose and morrhuate sodium), the patient reported significant improvements in pain and feelings of instability. (*C*) Twenty-two months after (*B*) (no intervening treatment) when the patient presented after a new injury to the contralateral knee. He reported that the knee had continued to improve after our last follow-up and the palpable cyst over the medial knee had gone away. The image confirmed resolution of the cyst and meniscofemoral ligament tear with return to normal fibrillar pattern and thickness in the MCL.

filling in a region of volume loss from tearing. This process may result in no overall change in tendon thickness, although the tendon health would be much improved. In development of future scales, it may be beneficial to grade tendinosis separately from tendon tears because tears do not always reflect underlying tendinosis.

Maxwell and colleagues[35] attempted to deal with this by developing a grading system similar to scales used to grade muscle strength on physical examination. Echogenicity and neovascularity were subjectively graded from 0 to 3. They also recorded presence or absence of anechoic regions, cortical irregularity at the tendon insertion, and intratendinous calcification. Irregularity at the enthesis and tendon calcification did not change after treatment. This finding is not surprising because the injections did not target these regions and there was no effort at tenotomy to break up calcifications. With dextrose prolotherapy, the anechoic clefts reduced by 78%, but the overall echogenicity improved in only 18% of patients. These findings are counterintuitive and may be the result of no true change in tissue density, targeting of injections only at the regions of anechoic signal or lack of sensitivity in the grading system itself.

Neovascularity was studied by Zanetti and colleagues.[43] In a study of 40 consecutive patients with Achilles tendinopathy, they found that neovascularization was a specific sign for pain, but it was not predictive of outcome using conservative treatment. However, tendon inhomogeneity (ie, loss of fibrillar pattern and/or scattered hypoechogenicity) was associated with unfavorable outcome in this population.

Other investigators have tried to quantify the extent of this inhomogeneity through more volumetric measures. Gemignani and colleagues[44] graded patellar tendinopathy in an athletic population using axial scans near the patellar origin, the classic location for pathology. They measured the volume of diseased tendon as a percentage of total tendon volume in the transverse plane by tracing an ellipse of the inhomogeneous regions. This was then graded from 1 to 3, whereas grade 4 was defined as partial or total tendon tear with partial or total tendon retraction seen on longitudinal images. Initial tendon grading was then correlated with abnormal neovascularity and prognosis for response to conservative therapy consisting of “mesotherapy, cicatrizing and vasodilator drugs, thermotherapy such as tecartherapy and hyperthermia, extracorporeal shock wave therapy, and rehabilitation.”

The use of ultrasound to enable us to see functional motion holds great potential for physicians focused on function. Moller and colleagues[45] studied the ultrasonographic and MRI appearance of the ruptured Achilles tendon with operative and nonoperative treatment. They found no statistically significant difference between the 2 groups on imaging abnormalities at 6 and 12 months after treatment, except that the nonoperative group showed fewer adhesions and less restriction in tendon gliding, findings that could only be evaluated with MSKUS.

### *Quantitative Ultrasound*

In work with the department of Physical Medicine and Rehabilitation at the University of Pittsburgh, motion/impingement scales were included in the development of an Ultrasound Shoulder Pathology Rating Scale (USPRS). Our goal was a more global measure of shoulder integrity, specifically as it relates to risk factors of rotator cuff disease in wheelchair users with spinal cord injury (SCI). Tendon grading focused on ability to identify fibrillar pattern in supraspinatus and long biceps tendon. We also graded subscapularis and supraspinatus impingement with active motion to better reflect actual shoulder function. These and other subscales were added to get a total numerical score. The USPRS was found to have external validity, correlating with age, duration of SCI, and weight. It also showed a positive trend in correlating with the Wheelchair User's Shoulder Pain Index (WUSPI).[46] A similar scale, the Ultrasound Elbow Pathology Rating Scale (UEPRS), has been developed for use in research of LE.

Truly quantitative measures would help to eliminate the subjectivity built into clinical quantitative grading systems such as the USPRS. Collinger and colleagues[47] developed a quantitative measure of fiber organization based on computerized analysis of gray-scale images. A second study has shown that tendinopathy of the biceps and supraspinatus tendon measured using the Quantitative Ultrasound Scale (QUS) correlates with higher scores on the USPRS.[48] These scales are the first to quantitatively measure shoulder pathology on ultrasonography. Computerized analysis of tendon organization has been used to evaluate tissue response to PRP in an equine model. Bosch and colleagues[49] showed that surgically created lesions in equine flexor tendons have improved tendon fiber alignment during healing if they are treated with PRP compared with a control injection. This type of quantitative measure needs to be applied in research on appropriately selected human patients with chronic tendinopathy.

Ultrasound elastography is a technique used in research to evaluate tissue strain and stiffness; some researchers have referred to this technique as an acoustic strain gauge. Physiatrists at the National Institute of Health are using a similar technique, vibration sonoelastography, to better identify and understand the pathophysiology of myofascial trigger points (MTrPs).[50] An early study has shown that clinically identified MTrPs show decreased vibration amplitude compared with adjacent normal muscle. Similar approaches may be useful to quantify tissue stiffness in regions of pathology where a loss of tension would be expected, such as muscle tears and tendinopathy.

## NEW CONCEPTS IN STRUCTURAL STABILITY

### *Investigational Uses of Ultrasonography in Soft Tissue Healing*

The American Heritage Dictionary defines physical medicine as "The branch of medicine that deals with the treatment, prevention, and diagnosis of disease by essentially physical means, including manipulation, massage, and exercise, often with mechanical devices, and the application of heat, cold, electricity, radiation, and water. Also called *physiatrics*, *physiatry*."[51] Understanding physical forces and their effects from the cellular level to the whole body level is fundamental to our profession. As shown in this review, ultrasonography is helping us to understand these physical forces and test old theories on how to physically stimulate repair in soft tissue.

Donald Ingber,[52] a vascular biologist, has advanced the understanding of cellular mechanotransduction, which is described as the mechanism by which cells convert mechanical signals into biochemical responses. Dr Ingber's career has elucidated the structural elements of the cell that convert physical force into chemical processes such as nuclear transcription. His primary conceptual model is based on tensegrity theory. Tensegrity, a combination of tension and integrity, is a term first proposed by Buckminster Fuller to describe stability in the sculptures of Kenneth Snelson.[53] Primary to this model is the presence of isometric tension, or prestress, which is maintained by compression and tension elements; individual cells can maintain their structure and respond effectively to their physical environment only if they have appropriately balanced tension from intact structural elements.

Stephen Levin[53] has proposed the term biotensegrity in understanding the dynamic stability of musculoskeletal structures. Stable biologic structures display a balanced tension that allows transfer and diffusion of stresses through the entire structure. He describes a system of continuous tension but discontinuous compression. In this construct, the bones are considered as compression elements that do not contact each other, thus these elements are discontinous. They are conceived as floating in the continuous tension network made of all the soft tissues, including ligaments, tendon, muscle, and fascia. His concepts add another dimension to physiatric concepts of the biomechanical chain, and are also consistent with the view of traditional osteopathic physicians and manual body workers that have always seen the body as an integrated unit in which the region of pain does not necessarily coincide with the structural deficit. Consequently a thorough evaluation of the entire musculoskeletal system requires development of a holistic view and advanced palpatory skills to discern tissue tension, edema, tenderness, and so forth.

Ultrasonography has the potential to extend these palpatory skills through the addition of dynamic tissue visualization into the diagnostic evaluation. The term sonographic palpation describes the use of the ultrasound probe to simultaneously observe tissue abnormalities while patients report sensitivity to pressure, such as a report of paresthesias with compression of an entrapped median nerve at the carpal tunnel. Tissue compressibility observed during dynamic ultrasonography can be used to subjectively evaluate tension in response to the pressure applied. Hands-on experience with MSKUS over years develops the same palpatory skills, potentially making diagnosis of muscle/fascial tears more accurate. This clinical skill can be used to observe response to treatment. In our experience, regions of myofascial tears seen on MSKUS display more MTrPs, as shown by increased twitch responses seen during

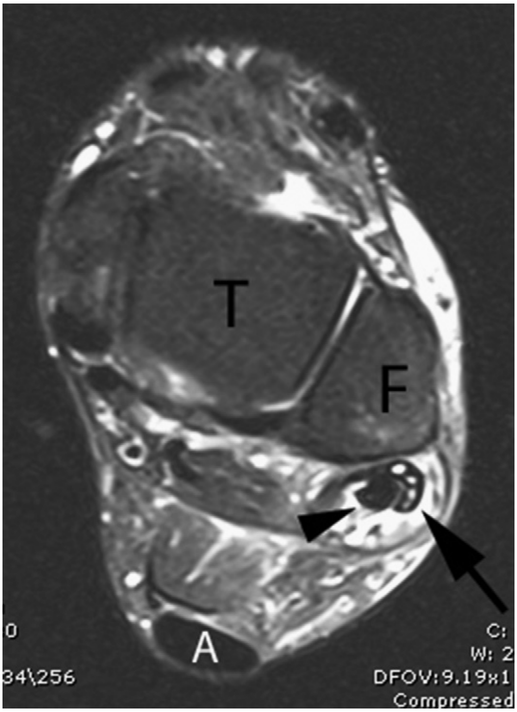

**Fig. 9.** Sixty-nine-year-old woman with peroneous brevis tendinopathy and tear on MRI axial view (T2, fat saturated). (*Arrow*) Peroneus brevis tendon with abnormal crescent shape and increased signal consistent with tear. (*Arrowhead*) Peroneus longus tendon. A, Achilles tendon; F, fibula; T, tibia.

percutaneous needling. This observation has implications when interpreted through the theoretic construct of tensegrity. Do MTrPs develop in muscles that have lost prestress through degradation/tearing of collagen in the fascial and endomysial layers? The next logical question for those interested in muscle needling techniques may then be the following: Does needling and/or injection of the myofascia stimulate repair of these tissues?

There are no published reports or studies on the use of needling with injection of hyperosmolar dextrose for the treatment of chronic muscle tears. A final case example may help in understanding this investigational technique. A 69-year-old woman was referred by a podiatrist to consider prolotherapy for a peroneal tendon tear. The MRI scan in **Fig. 9** shows an abnormal, crescent-shaped peroneus brevis tendon with tears and synovitis. She was treated with 25% dextrose prolotherapy to ankle ligaments and the peroneal tendon directly via ultrasound guidance. After 3 monthly treatments, she reported significant decrease in pain and episodes of swelling over the peroneal tendon; however, she still had feeling of ankle weakness and instability with activity. **Fig. 10** shows improvement in ultrasonographic appearance of the peroneal tendons after treatment. Ultrasound examination of the calf revealed diffuse disorganization of the medial soleus muscle. Needle fenestration using a 25-gauge, 5-cm needle with infusion of 15% dextrose was performed through the superficial and deep fascial layers of the medial soleus each month for a total of 4 treatments. At the second treatment to the soleus, she remembered that she had an episode of

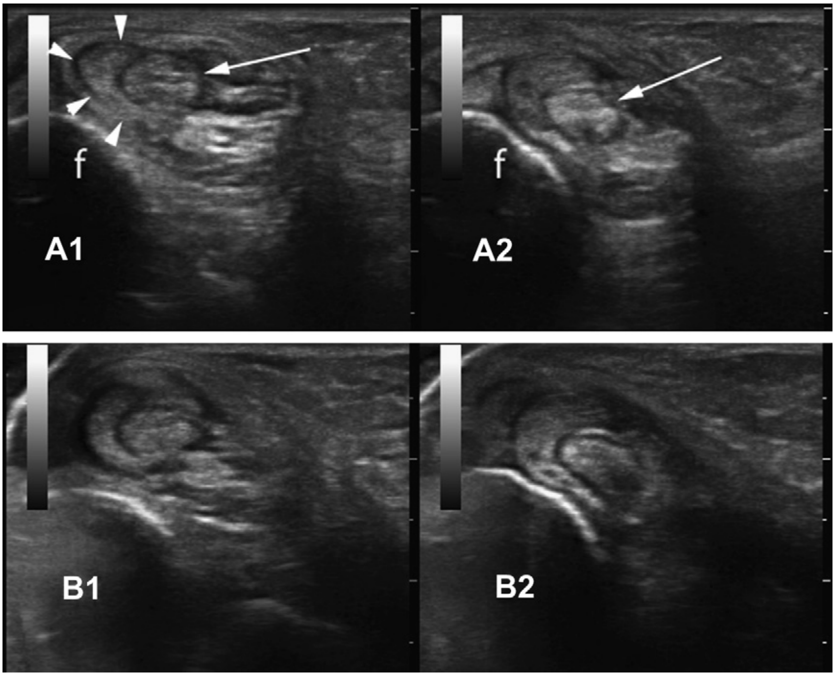

**Fig. 10.** Same patient as **Fig. 9**. Ultrasound imaging pre- and posttreatment with 25% dextrose injection. (*A1*, *A2*) Transverse slices through the peroneal tendons. Multiple arrowheads outline the abnormal crescent-shaped peroneus brevis that partially encircles the peroneus longus. (*B1*, *B2*) are the same slices after treatment; the tendons have improved definition and homogeneity.

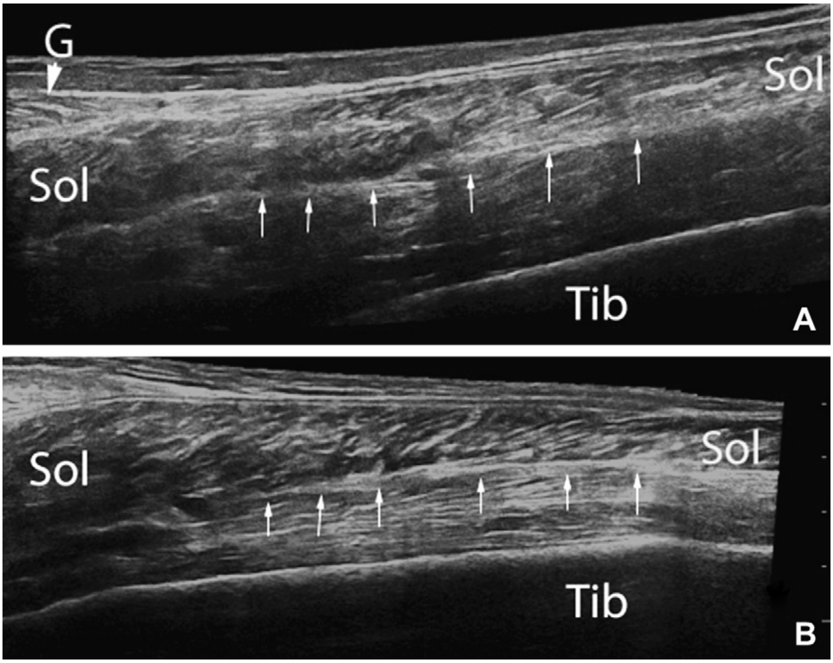

**Fig. 11.** Same patient as Figs. 9 and 10. Extended field of view images of medial soleus pre- and posttreatment with 15% dextrose. (*A*) Loss of normal muscle architecture and disorganization of the fascial tissues. (*B*) Same location 6 weeks after her last treatment. Muscle and fascial definition have both improved. Arrows outline the deep fascia of the soleus. G, distal gastrocnemius muscle; Sol, soleus muscle.

Achilles tendinosis 3 years before (confirmed by MRI). Since then she had ankle weakness and pain with stairs, gardening, and walking. Movie 4 shows a twitch response during needling and injection of the soleus. **Fig. 11** shows the change in muscle definition on extended field-of-view imaging 6 weeks after the fourth treatment. At follow-up 8 months after her last treatment, she reported 90% improvement in her ankle symptoms that had been present for more than 3 years.

## SUMMARY

Ultrasonography expands our ability to understand degeneration and injury of tendon, ligament, and other myofascial structures that likely contribute to pain and disability. Prolotherapy, using a broad array of substances, has been described historically as regenerative injection therapy without high-level evidence of clinical efficacy or that tissue regeneration actually takes place. Increased publication of studies on prolotherapy and the advent of platelet-rich plasma as another possible injectant have increased interest in this controversial procedure. Double-blind placebo-controlled studies of injection are difficult to design for the same reasons that surgical studies are difficult to design; the patient knows whether or not injection took place. Perhaps more importantly, there is a potential therapeutic effect in simple needling/percutaneous tenotomy and injection of any substance (even normal saline). MSKUS now provides a more objective tool for evaluating tissue response to all types of injection techniques. The cases documented here show clear tissue repair on ultrasound in individual cases of prolotherapy treatment. It is highly unlikely, but theoretically possible, that each of these cases repaired spontaneously and was unrelated to the clinical intervention. Assuming that these individual cases repaired in response to the prolotherapy, it is still scientifically unproven that most patients will respond to prolotherapy with tissue repair evident on ultrasonography. Development of quantitative ultrasound tools and the use of these tools in large, controlled studies could greatly improve research in regenerative injection techniques.

## APPENDIX SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at DOI:10.1016/j.pmr.2010.06.003.

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